UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Note to Reader
January 8, 1998

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply. EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, If unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues available in the information docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack E. Housenger, Acting Director
Special Review and Reregistration Division

MEMORANDUM

SUBJECT: **PIRIMIPHOS-METHYL:** Toxicology Chapter of the Registration Eligibility Document

FROM: Sanju Diwan, Ph.D.
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THROUGH: Alberto Protzel, Ph.D.
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TASK ID: DP Code: D244375 Submission: S521061
Case: 2535 PC Code No.: 108102

REGISTRANT: Wilbur-Ellis Company

ACTION REQUESTED: Prepare a toxicology chapter for pirimiphos-methyl.

RESPONSE: Based on the currently available toxicology data on pirimiphos-methyl, a toxicology chapter has been prepared and is attached.

I. HAZARD CHARACTERIZATION

Pirimiphos-methyl is an organophosphate. The toxicology database provides an overwhelming evidence confirming its anticholinesterase activity in various species including humans, rabbits, guineapigs, rats and mice. It causes dose-related inhibition in plasma, RBC and brain cholinesterase (ChE) activity by all routes of exposure and following exposure for various durations. Females appear to be more susceptible than males. The clinical symptoms produced include tremors, ataxia, leg paralysis, abnormal gait, salivation etc. However, none of the studies have revealed changes in brain weight or histopathology. ChE inhibition occurs at very low dose levels and is reversible when exposure is discontinued. Younger rats are equally susceptible to ChE inhibition as older rats. There appears to be no increase in sensitivity among fetuses or pups following pre- and/or post-natal exposure to this compound. Pirimiphos-methyl is extensively metabolized and rapidly excreted by mammals and does not accumulate in the tissues. While low levels of the parent compound and its metabolites were found in the animal tissues, the predominant metabolites are non-ChE inhibiting hydroxypyrimidines that are less acutely toxic than the parent compound. None of the dephosphorylated metabolites in mammalian tissue or urine is a ChE inhibitor. The oxygen analog, O-(2-ethylamino-6-methyl-pyrimidin-4-yl) O,O-dimethyl phosphorothioate), is the only phosphorus-containing metabolite that has the potential for inhibiting cholinesterase. The available studies on pirimiphos-methyl are summarized in Table 1.

A. ACUTE TOXICITY

The Agency granted a waiver from the requirement of conducting acute toxicity studies on technical pirimiphos-methyl and has acceptable acute toxicity studies on 75% formulation (EPA, 1992) In rats, pirimiphos-methyl is acutely toxic via the dermal route of exposure but has low toxicity via the oral and inhalation routes of exposure. It causes eye and skin irritation in rabbits (Refer to Table 2).

The estimated acute oral LD_{50} for pirimiphos-methyl (75% a.i.) in rats is 2.4 g/kg (2.1 to 2.8 g/kg) (Toxicity Category II; Guideline 81-1; MRID # 00126257).
The acute dermal LD_{50} value for pirimiphos-methyl (75% a.i.) in rabbits was >3.2 ml/kg (3.5 g/kg) for females and between 2.0-3.2 ml/kg for males (2.2-3.5 g/kg) (Toxicity Category III; Guideline 81-2; MRID # 00126257).

The acute inhalation LC_{50} pirimiphos-methyl (90.6% a.i.) was >5.04 mg/L (analyzed concentration 4.7 mg/L; Toxicity category IV; Guideline 81-3; MRID # 41556304). Pirimiphos-methyl is irritating following ocular exposure. In a primary eye irritation study, pirimiphos-methyl (75% a.i.) produced reversible opacity in the rabbit eye (Toxicity Category II; Guideline 81-4; MRID 00126527). A primary dermal irritation study with the 75% formulation of pirimiphos-methyl showed that it causes moderate irritation at 72 hours in rabbits (Toxicity Category III; Guideline 81-5; MRID 00126257). The dermal sensitization studies in guinea pigs using pirimiphos-methyl (75% formulation) showed

that the compound is not a skin sensitizer (Guideline 81-6; MRID 00126257; 00129341).

TABLE 1. Toxicology Profile for Pirimiphos-methyl

Guideline #	Study Type	MRID #	Required	Satisfied
81-1	Acute oral - rats	00126257	Yes	Yes
81-2	Acute dermal - rabbits	00126257	Yes	Yes
81-3	Acute inhalation - rats	41556304	Yes	Yes*
81-4	Primary eye irritation - rabbits	00126257	Yes	Yes
81-5	Primary dermal irritation - rabbits	00126257	Yes	Yes
81-6	Dermal sensitization - guinea pigs	00126257	Yes	No
82-1	Subchronic feeding - rats	00129343	Yes	No
82-1	Subchronic feeding - dogs	00080743	Yes	No
82-2	21-Day dermal - rabbits	00129342	Yes	No
83-5	Chronic toxicity/Carcinogenicity - rats	92147035	Yes	No
83-1(b)	Chronic toxicity - dogs	92147036; 92147014	Yes	No
83-2(b)	Chronic Toxicity/Carcinogenicity - mice	43968401	Yes	Yes
83-3(a)	Developmental toxicity - rats	00151623	Yes	No
83-3(b)	Developmental toxicity - rabbits	43726801	Yes	Yes
83-4	3-Generation reproduction - rats	92147035	Yes	Yes
84-2(a)	Gene mutation	00144969	Yes	Yes
84-2(b)	In vivo cytogenetics assay	41599501	Yes	Yes
84-2	Structural chromosomal aberrations	00126256	Yes	Yes
84-4	Other mutagenic mechanisms:			
	Mouse lymphoma assay	41556303	Yes	Yes
	Sister-chromatid exchange assay	41599502	Yes	Yes
	Dominant Lethal Assay	41556302	Yes	No
85-1	Metabolism	00047987	Yes	Yes**
81-7	Acute delayed neurotoxicity - hen	- -	Yes	No
81-8	Acute neurotoxicity - rats	43594101	Yes	Yes
82-5	Subchronic delayed neurotoxicity - hen	00126254	Yes	No
82-7	90-Day subchronic neurotoxicity - rats	43608201	Yes	Yes

* With the exception of the acute inhalation study, all other acute toxicity studies were conducted on the 75% formulation.

** Tissue retention study

Acute Toxicity Profile

GDLN	MRID	Study Type	Species	Results	Tox Category
81-1	00126257	Acute Oral	rat	LD_{50} = 2.4 g/kg	II
81-2	00126257	Acute Dermal	rabbit	LD_{50} = >3.5 g/Kg for females and between 2.2-3.5 g/Kg for males	III
81-3	41556304	Acute Inhalation	rat	LC_{50} = >4.7 mg/L	IV
81-4	00126257	Primary Eye Irritation	rabbit	Irritant	II
81-5	00126257	Primary Skin Irritation	rabbit	Moderate Irritant	III
81-6	00126257	Dermal Sensitization	guinea pig	Non-sensitizer	N/A

N/A = Not applied; * With the exception of these two studies all other acute toxicity studies were conducted on the 75% formulation of pirimiphos-methyl.

B. SUBCHRONIC TOXICITY

Although the studies summarized below are unacceptable and/or nonguideline studies, they provide overall weight-of evidence for anticholinesterase activity of this compound in various species.

28-Day Human Oral Study

In a repeated dose study in humans, pirimiphos-methyl (97.8% a.i.) was administered daily to 5 healthy adult human males by gelatin capsule at a dose level of 0.25 mg/kg/day for 28-days. The NOEL (threshold) is 0.25 mg/kg/day based on marginal, transient depressions in plasma cholinesterase in one male. The LOEL is >0.25 mg/kg/day. This study was not conducted to satisfy guideline data requirements for pirimiphos-methyl. However, it provides useful information for evaluation of human hazard assessment and supports findings of a subsequent 56-day study in humans (Accession 097671).

56-Day Human Oral Study

In the subsequent study, pirimiphos-methyl (97.8% a.i.) was administered daily to 3 healthy adult human males and 4 females by gelatin capsule at a dose level of 0.25 mg/kg/day for 56 days. Two additional females were administered blank capsules as

controls during this time. The NOEL (threshold) is 0.25 mg/kg/day, based on marginal, transient decreases in plasma cholinesterase activity in 3 females from study Day 14 onwards. Therefore, the LOEL is 0.25 mg/kg/day. This study is classified as

Unacceptable/Nonguideline (MRID 00080732).

28-Day Rat Feeding Study

In a 28-day feeding study, pirimiphos-methyl (97.0% a.i.) was administered to three groups of SPF-Wistar rats (12/sex/dose/group) at dose levels of 0, 5, 8, 10 or 50 ppm (equivalent to 0, 0.25, 0.4, 0.5 or 2.5 mg/kg/day, respectively) for 28 days. The purpose of the study was to determine the sensitivity of younger rats (approx. 6 week old) for ChE inhibition (5/sex/group) in comparison to that determined in older rats (>12 week old) in other studies. The LOEL was 50 ppm (2.5 mg/kg/day) based on plasma ChE inhibition in both sexes. The NOEL was 10 ppm indicating no differential sensitivity from older rats (NOEL for ChE Inhibition= 8-10 ppm or 0.4-0.5 mg/kg/day). this study is classified as Unacceptable/Nonguideline (MRID 00129343)

13-Week Dog Oral Study

In a thirteen week study, pirimiphos-methyl (% a.i. not reported) was administered to four groups of beagle dog (4/sex/dose) at dose levels of 0, 2, 10 or 25 mg/kg/day in a corn oil capsule once daily, seven days/week for thirteen weeks. The doses were selected based on the results of a preliminary study in which a dose of 50 mg/kg/day was severely toxic to dogs. A reversible and non-progressive inhibition of plasma ChE and dose-related inhibition in RBC ChE levels were noted in both sexes at all dose levels ($\geq$20% beginning Week 1). No significant effect on brain ChE level was observed. However, the data are questionable because the post-mortem to assay time was not reported. The systemic toxicity LOEL was 2 mg/kg/day based on plasma and RBC ChE inhibition in both sexes. The NOEL was <2 mg/kg/day. This study is classified as Unacceptable/Guideline and does not meet the requirement of a subchronic toxicity study in dogs (82-1) (MRID 00080743).

21-Day Rabbit Dermal Toxicity

In a 21-day dermal toxicity study, three groups of 10 New Zealand white rabbits (5/sex) per group were treated with intact skin and three groups of 10 rabbits (5/sex) per group were treated with abraded skin at dosages of 4, 40 or 400 mg/kg/day of pirimiphos-methyl (90.6%) in propylene glycol six hours per day, five days/week for a total of 15 applications over a three week period. The systemic toxicity LOEL is 4 mg/kg/day based on RBC ChE inhibition in females with intact (21%) or abraded (23%) skin. The systemic toxicity NOEL is <4 mg/kg/day. The dermal toxicity LOEL is 400 mg/kg/day for males and females based on the findings of skin reactions; the dermal toxicity NOEL is 40 mg/kg/day for males and females. This study is classified as Unacceptable/guideline and does not meet the requirements of a 21-day dermal toxicity study in rabbits (82-2) (MRID 00129342)

C. CHRONIC TOXICITY AND CARCINOGENICITY

The available studies in dogs, rats, and mice are inadequate to assess the chronic toxicity

of pirimiphos-methyl.

Chronic Toxicity Study in Dogs

In a chronic toxicity study, pirimiphos-methyl was administered to four beagle dogs/sex/dose in gelatin capsules at dose levels of 0, 0.5, 2, or 10 mg/kg/day for two years. Numerous study deficiencies were identified in this study. While previous issues have been raised by HED about the significance of reported findings at the 0.5 mg/kg/day dose level, these effects may in reality be occurring at much lower dose levels than the reported nominal dosages which are likely varying significantly over time due to stability problems, batch and test sample changes. Based upon the findings, the LOEL for brain and plasma ChE inhibition is $\leq$ 0.5 mg/kg/day and no NOEL was determined; the LOEL for RBC ChE inhibition is 2 mg/kg/day and the NOEL is 0.5 mg/kg/day. The systemic NOEL is 0.5 mg/kg/day and the LOEL is 2 mg/kg/day based on clinical sign (semi-liquid stool). This study is classified as Unacceptable/Guideline and does not meet the requirements of a chronic toxicity study in dogs (83-1b) (MRID 92147036/92147014).

Combined Chronic Toxicity and Carcinogenicity Study in Rats

In a combined chronic toxicity/carcinogenicity study, Wistar (SPF) rats (72/sex/group) were administered pirimiphos-methyl via diet at dose levels of 0, 10, 50, or 300 ppm (equivalent to 0, 0.4, 2.1, or 12.6 mg/kg/day) for two years.The dosing was considered to be adequate to evaluate the systemic and carcinogenic potential of pirimiphos-methyl. Dose-related and progressive plasma and brain ChE inhibitions were seen at 50 and 300 ppm. RBC ChE inhibition was observed at 300 ppm at various time points. There were no effects on body weight, food consumption and hematology. No clinical chemistry data were available. Of the 42 high-dose male rats, there were pancreatic islet cell adenomas in 4 rats and a carcinoma in one rat compared to 0/42 control male rats. In addition to several study deficiencies, no individual animal data for tumors and neoplastic microscopic findings were submitted. Therefore, the carcinogenicity of pirimiphos-methyl can not be assessed due to insufficient data submitted. Under conditions of this study, the NOEL for systemic toxicity was 300 ppm (12.6 mg/kg/day) (the highest dose tested). The NOEL for plasma and brain ChE inhibition was 10 ppm (0.4 mg/kg/day) and the LOEL was 50 ppm (2.1 mg/kg/day). The NOEL for RBC ChE inhibition was 50 ppm (2.1 mg/kg/day) and the LOEL was 300 ppm (12.6 mg/kg/day). this study is classified as Unacceptable/Guideline and does not meet the requirements of a chronic toxicity study in rats (83-5b) (MRID 92147035).

Carcinogenicity Study in Mice

In a mouse carcinogenicity study, pirimiphos-methyl (86.7% a.i., Lot# RS492/B; 89.8% a.i., Lot# 20307-00S) was administered to 50 CD-1 mice/sex/dose at dose levels of 0, 50, 200, or 400/300 ppm (0, 8.3, 33, or 52 mg/kg/day for males and 0, 9.7, 39, or 61 mg/kg/day for females) for 78 weeks. A satellite study was concurrently run using 10 mice/sex/dose but for 52 weeks. The initial 400 ppm dose resulted in excessive toxicity and moribundity and was reduced to 300 ppm after 8 days. At 200 ppm mean initial body weight in males was decreased (≈9%), $p<0.001$) and clinical signs (piloerection, hunched posture, dark eyes and hyperactivity) were noted in both sexes. At 300 ppm male body weight was decreased at most intervals and clinical signs were more frequent. The LOEL for systemic effects is 200 ppm (33♂ and 39♀ mg/kg/day) based on body weight effects and clinical signs. The NOEL is 50 ppm (8.3♂ and 9.7♀ mg/kg/day).

At 50 ppm, inhibition of plasma (88%♂ and 93% ♀) and RBC ChE (57%♂ and 48%♀) and brain AChE (21%♂, $p < 0.05$) was evident at week 52 and a similar pattern was evident at week 78. Higher dose levels had progressively more inhibition. The LOEL for ChE inhibition is 50 ppm (8.3♂ and 9.7♀ mg/kg/day) based on depressed plasma, RBC and brain ChE. The NOEL for ChE is < 50 ppm. Dosing was considered adequate based on the need to reduce the high dosage from 400 ppm to 300 ppm after 8 days in order to avoid extreme toxicity and excessive mortality and the consistent inhibition of ChE/AChE at all dose levels. Under the conditions of this study, there was no evidence of a carcinogenic effect of pirimiphos-methyl in mice. This study is classified as Acceptable/Guideline and satisfies the guideline requirements of a chronic toxicity study in mice (83-2b) (MRID 43968401). In another mouse carcinogenicity study, pirimiphos-methyl (97.8% a.i.) was administered in corn oil to 52 CFLP mice/sex/group at dietary levels of 0, 5, 250 or 500 ppm (equivalent to 0, 0.5, 25.9 or 45.0 mg/kg/day for males and 0, 0.6, 27.6 or 50.6 mg/kg/day for females, respectively) for 80 weeks. With the exception of 250 ppm dose group, each group consisted of 12 additional animals for cholinesterase determination. The test diet for the highest dose groups initially contained 300 ppm of the test compound (the duration of treatment was not specified). The dose was then increased weekly by 50 ppm to 500 ppm. No brain ChE levels were measured. At 500 ppm, non-progressive but marked and consistent dose-related inhibition of activity was noted in RBC ChE (84% in males and 86% in females) and plasma ChE (83% in males and 85% in females). At 5 ppm, there was non-significant inhibition in RBC ChE (30% in males only) while only borderline but statistically significant inhibition of plasma ChE activity (10% in males and 22 % in females) was noted compared to controls. Gross and histopathological examination provided no evidence indicating altered spontaneous tumor profile of the CFLP mouse. The systemic LOEL was 5 ppm based on RBC ChE inhibition in males (0.5 mg/kg/day) and plasma ChE inhibition in females (0.6 mg/kg/day). No NOEL was established. This study is classified as Unacceptable/guideline and does not satisfy the guideline requirements of a carcinogenicity study in mice (83-2b) (MRID 92147032). This requirement is already satisfied by the recent mouse study with MRID 43968401.

D. REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDIES

Sufficient data are available to assess the reproductive and developmental toxicity for pirimiphos-methyl. In the prenatal developmental toxicity and reproduction studies, maternal/parental NOELs were less than or equivalent to offspring NOELS. No CNS malformations were noted in fetuses or pups. Based on the comparison of the NOELS and LOELS for maternal/parental and developmental toxicity, no increased sensitivity was noted among fetuses or pups. In a dominant lethal assay, pirimiphos-methyl did not induce pre-and post-implantation losses. Furthermore, no differences in sensitivity for ChE inhibition were noted among younger rats compared to older rats.

Reproductive Toxicity Study in Rats

In a 2-generation reproduction study, pirimiphos-methyl (86.7% a.i.) was administered to male and female Sprague-Dawley CD rats in the diet at concentrations of 0, 10, 40, or 160 ppm (corresponding to 0.87, 3.43 or 13.72 mg/kg/day in males and 0.98, 3.88 or 15.41 mg/kg/day for females for the premating periods).

There were no effects on reproductive parameters of either generation and there were no clinical signs. The LOEL for systemic and reproductive toxicity is > 160 ppm (13.72 mg/kg/day for males and 15.41 mg/kg/day for females). The NOEL for systemic and reproductive toxicity is ≥ 160 ppm (13.72 mg/kg/day for males and 15.41 mg/kg/day for females).

Plasma ChE was significantly ($p \leq 0.01$) reduced in a dose-related manner at 10 ppm (22% in males and 39% in females) and above (up to 52% in males and 83% in females) in the F_o groups. In the F_1 groups, only females (35%) were inhibited at 10 ppm but inhibition was consistent at higher doses. RBC ChE was significantly ($p \leq 0.05$ or 0.01) reduced at 40 ppm (≈22% in males and 11% in females) and 160 ppm (36% in males and 48% in females) for the F_0 groups. The F_1 groups showed lesser inhibition. Brain ChE was statistically significantly inhibited ($p \leq 0.05$ or 0.01) in females only at 40 ppm (26% in F_0 and 16% in F_1) and 160 ppm (53% in F_0 and 44% in F_1). The LOEL is 10 ppm (0.87 mg/kg/day for males and 0.98 mg/kg/day for females) based on inhibition of plasma ChE. The NOEL was <10 ppm (0.87 mg/kg/day for males and 0.98 mg/kg/day for females). The study is classified as Acceptable/Guideline and satisfies the guideline requirements of a 2-generation reproductive toxicity study (83-4) in rats (MRID 43726801)

Developmental Toxicity Study in Rats

Four groups of twenty-four mated female Alpk:AP (Wistar-derived) rats were administered pirimiphos-methyl (88.5% a.i.) in corn oil by gavage at dose levels of 0, 1.5, 15, or 150 mg/kg/day from gestational days 7–16, inclusive. A single treatment-related mortality occurred at 150 mg/kg/day. Twenty of the twenty-three surviving rats showed some signs of toxicity including abnormal gait, changes in behavior, irregular respi-ration, urinary incontinence and body tremors. During dosing and post-dosing periods, reduction in body

weight gain (57 and 22%, respectively) accompanied by decrease in food consumption (15 and 30%, respectively) were noted in dams. No significant toxi-cological effects were observed at 15 mg/kg/day. However, in the absence of individual animal data the maternal findings could not be confirmed. Consequently, the maternal LOEL and NOEL could not be determined. There are no developmental effects noted in the study at doses up to 150 mg/kg/day. However, in the absence of data on indi-vidual fetuses and litters, the lack of developmental findings could not be confirmed. Consequently, the developmental LOEL and NOEL could not be determined. This study is classified as Unacceptable/Guideline and does not satisfy the guideline requi-rements of a developmental toxicity study (83-3a) in rats (MRID 00151623).

Developmental Toxicity Study in Rabbits

Four groups of New Zealand White rabbits were dosed at levels of 0, 12, 24 or 48 mg/kg/day of pirimiphos methyl in corn oil (a.i.) on days 6 through 18 of gestation. Their pups were delivered by caesarian section on day 29. The only toxic response evident was inhibition of plasma ChE (37%) and RBC ChE (44%) at 24 mg/kg/day. Higher levels of inhibition were noted at 48 mg/kg and brain AChE (38%) was also inhibited. There were no other indications of maternal toxicity and there were no indications of effects on fetal development. The LEL is 24 mg/kg-bw/day based on ChE inhibition and the NOEL is 12 mg/kg-bw/day for maternal toxicity. The LOEL for developmental toxicity is > 48 mg/kg-bw/day and the NOEL is ≥ 48 mg/kg/day. This study is classified as Acceptable/Guideline and satisfies the guideline requirements of a developmental toxicity study (83-3b) in rabbits (MRID 43206301)

E. NEUROTOXICITY

A data gap exists for an acute delayed neurotoxicity study in hens. Some evidence of delayed neurotoxicity was noted in hens following repeated exposure to pirimiphos-methyl. In rats, acute or repeated exposure to pirimiphos-methyl causes cholinergic signs and decreases in plasma, RBC and brain ChE. However, no changes in brain weight or histopathology were observed.

In a subchronic delayed neurotoxicity study, groups of 10 hens received 0.5, 1.0, 2.5, 5.0 and 10.0 mg/kg/day pirimiphos-methyl (93.5%) by gavage daily for a total of 90 doses. Two Additional groups received 5.0 or 10.0 mg/kg/day (total of 90 doses) followed by a recovery period of 30 days. At 10 mg/kg/day, the clinical signs were seen even during the recovery period. Histopathology revealed neuropathological changes (Grade III) in one out of 6 hens from non-recovery group that received continuous dosing; histopathology was not performed on the recovery group. No NTE measurements were made. The birds in the recovery groups regained their body weight. TOCP (tri-ortho-cresyl-phosphate) treated controls had well defined ataxia, decreased body weight and food consumption, and axonal degeneration in the spinal cord. Based on equivocal evidence of histopathological lesions, the LOEL for delayed neurotoxicity was 10 mg/kg/day. The NOEL was 5 mg/kg/day. The study was unacceptable because the dosing was intermittent

for some animals. At 10 mg/kg/day, the non-recovery group animals had less severe and less frequent signs of toxicity compared to those that were seen in recovery group animals. At 10 mg/kg/day (non-recovery group) some animals that died earlier did not receive sufficient dosing and therefore, the histopathological examination did not revealed the treatment-related effects. This study was classified as Unacceptable/Guideline because of intermittent dosing of some animals and does not satisfy the guideline requirements for a delayed neurotoxicity study (82-5) in hens (MRID 00126254).

In an acute neurotoxicity study, 4 groups of 17 Sprague-Dawley Crl:CD^{R}BR strain rats/sex were dosed by gavage with pirimiphos methyl (89.8%) in corn oil at 0, 15, 150 or 1500 mg/kg/day. Clinical signs observed included clonic convulsions (all rats) and related parameters (impaired mobility, decreased rearing, decreased rotarod performance, posture changes), ocular effects such as alterations in pupil response, palpebral closure and exophthalmus), altered fur appearance (all animals) and lacrimation and salivation, decreased grip strength and decreased body temperature (up to 2.3 degrees in females). The LEL for neurotoxicity is 1500 mg/kg based on convulsions and other parameters. The NOEL is 150 mg/kg. Definite conclusions regarding brain regional susceptibility of AChE could not be drawn. After 24 hours at 15 mg/kg, plasma ChE inhibited 48% in females and 21% in males ($P<0.01$) and mid-brain AChE was inhibited 10% ($p<0.05$). The LOEL for plasma, RBC and brain ChE inhibition is 15 mg/kg and this level is considered a threshold for brain AChE. The NOEL is $\leq$15 mg/kg/day. This study is classified as Acceptable/Guideline and satisfies the guideline requirement for acute neurotoxicity study (81-8) in rats (MRID 43594101)

In a subchronic neurotoxicity study, Sprague-Dawley Br strain rats, 10/sex/group were dosed as control, 3, 30 of 300 ppm (corresponding to 0.2, 2.1 and 21.1 mg/kg/day for males and 0.2, 2.4 and 24.7 mg/kg/day for females) of pirimiphos methyl (89.8%) in their diets for 90 days. No neurotoxicity or systemic reactions were noted. The LOEL for neuro and systemic toxicity is $>$ 21.1 and $>$ 24.7 mg/kg/day (HDT) for males and females, respectively. The NOEL is $\geq$ 21.1 and $>$ 24.7 mg/kg/day for males and females respectively. The LOEL is 0.2 mg/kg/day based on plasma ChE inhibition; the NOEL is $<$0.2 mg/kg/day (LTD). The threshold NOEL/LOEL for RBC ChE inhibition is 2.1 and 2.4 mg/kg/day for males and females, respectively. The LOEL definitive LOEL for brain ChE inhibition is 21.1 and 24.7 mg/kg/day for males and females, respectively. This study was classified as Acceptable/Guideline and satisfies the guideline requirement for subchronic neurotoxicity study (82-7) in rats (MRID 43608201).

The Health Effects Division (HED) Hazard Identification Science Review Committee (Hazard ID SARC) determined that the available studies are inadequate to assess the neurotoxic potential of pirimiphos-methyl due to an existing data gap for Acute Delayed Neurotoxicity Study in Hens (§81-7), Chronic Toxicity Study in Dogs (§83-1) and a Chronic Toxicity/Carcinogenicity Study in Rats (§83-5). Due to the existing dat gaps of critical studies (listed above), the Committee was unable to determine whether or not a developmental neurotoxicity study would be required. Consequently, this data

requirement was placed in a reserve status pending receipt of the critical studies.

F. MUTAGENICITY STUDIES

Sufficient data are available to satisfy the data requirements for mutagenicity testing. With the exception of the dominant-lethal assay, all other studies are acceptable. The available studies submitted to the Agency in conjunction with the published data indicate that pirimiphos-methyl is not mutagenic in bacteria or cultured mammalian cells. Pirimiphos-methyl did, however, induce SCE in vitro but was not clastogenic either in vitro or in vivo and was not genotoxic in primary rat hepatocytes. The data suggest, therefore, that the genotoxic activity demonstrated in the SCE assay is not expressed in vivo. Confidence in this conclusion is high since the suggestive evidence of test material interaction with the target cells noted in the submitted bone marrow cytogenetic assay was supported by the findings of Rajani et al (1986). Based on these considerations, the Hazard ID SARC (meeting of January 12, 1998) concluded that there is no concern for mutagenicity at this time. Five acceptable studies were available for review; summaries of these studies with MRID/Accession and/or Document Control Numbers follow:

1) Salmonella typhimurium reverse gene mutation assay: Independent trials were negative up to the highest concentration tested (5000 µg/plate +/-S9). This study was classified as Acceptable/Guideline and satisfies the guideline requirement for a microbial gene mutation assay (84-2) (MRID 00144969).

2) Mouse lymphoma $TK^{+/-}$ forward gene mutation assay: Independent trials performed using a microsuspension technique were negative up to a concentration that was lethal in the absence of S9 activation and moderately cytotoxic in the presence of S9 activation (200 µg/mL). This dose was also the maximum soluble concentration that could be achieved in the aqueous tissue culture medium. This study was classified as Acceptable/Guideline and satisfies the guideline requirement for an in vitro gene mutation in cultured mammalian cells (84-2) (MRID 41556303).

CHROMOSOME ABERRATIONS

3) In vitro chromosome aberrations in human lymphocytes assay : The test was negative up to cytotoxic concentrations ($\geq$116 µg/mL -S9; $\geq$289 µg/mL +S9). This study was classified as Acceptable/Guideline and satisfies the guideline requirement for an in vitro cytogenetic assay (84-2) (MRID 41599501).

4) In vivo bone marrow cytogenetic assay: The test was negative in CD-1 male mice receiving single oral gavage administrations of pirimiphos methyl ranging from 38-192 mg/kg (actual concentrations, based on analytical results) or exposed to 24-234 mg/kg/day (actual concentrations, based on analytical results) once daily for 5 consecutive days. Lethality and other clinical signs of toxicity were noted at the highest dose tested (HDT) in the multiple exposure dosing regimen. There was also suggestive evidence of bone marrow cytotoxicity at the HDT following multiple exposures. This study was classified

as Acceptable/Guideline and satisfies the guideline requirement for an in vivo cytogenetic assay (84-2) (MRID 00126256)

OTHER MUTAGENIC MECHANISMS

5) In vitro sister chromatid exchange (SCE) in Chinese hamster lung fibroblasts (Don cells) assay: The test was positive. Significant but not dose-related increases in the frequency of SCEs were obtained at 0.14-29 µg/mL without S9 activation. In the presence of S9 activation, the response was significant and dose-related at 14-145 µg/mL. Higher levels (≥145 µg/mL +/-S9) were severely cytotoxic and mitotic delay was seen at ≥0.29 µg/mL -S9 and ≥2.9 µg/mL +S9. This study was classified as Acceptable/Guideline and satisfies the guideline requirement for an in vitro mammalian cell sister chromatid exchange assay (84-2) (MRID 41599502).

Other Information: In addition to the Acceptable studies, an Unacceptable and not upgradable negative mouse dominant lethal assay (MRID 41556302) was submitted. Studies found in the open literature indicated that pirimiphos-methyl was negative in the S. typhimurium reverse gene mutation assay and did not induce micronuclei in rat hepatocytes in vitro. Similarly, Rajini et al (1986) found no evidence of micronuclei induction in Swiss male mice administered oral doses of pirimiphos-methyl up to 400 mg/kg once daily for 2 days. The HDT in this study was clearly cytotoxic to the target organ.

The submitted test battery satisfies the pre-1991 and the new mutagenicity initial testing battery guidelines. No further studies are required at this time.

G. METABOLISM

Pirimiphos-methyl is rapidly absorbed, metabolized and excreted in rats and dogs. In both species, 2-ethylamino-4-hydroxy-6-methylpyrimidine is the major metabolite. The metabolism of pirimiphos-methyl involves extensive cleavage of P-O bond followed by N-dealkylation and/or conjugation resulting in a loss of pyrimidine group. In rats given a single oral dose of (2-^{14}C-pyrimidine) labelled pirimiphos-methyl at 7.5 mg/kg, there was rapid uptake of radioactivity into the blood and was followed by its subsequent disappearance from the blood (MRID 00080739). Greater than 50% of the radioactivity present in the blood, 30 minutes after the dosing, had disappeared 1-hr post-dosing. Further, daily dosing of the labelled compound for a subsequent 3 days did not increase the total radioactive residues in the blood. When administered for 4 days, total radioactive residues in the liver, kidney and fat did not exceed 2 mg/kg pirimiphos-methyl equivalents. Only small amounts of unchanged parent compound were detected in the fat (0.15 mg/kg) and in the liver and kidneys (0.1 mg/kg). These studies provide no evidence of accumulation of parent or metabolites in the liver, kidney or adipose tissue of rats following daily dosing with pirimiphos-methyl over 4 days.

When rats were administered 0.6 mg/kg of ^{14}C-ring (2-C^{14}-pyrimidine) labelled pirimiphos-

methyl orally or intraperitoneally, 73-81% of the dose was excreted in the urine within the first 24 hours, indicating rapid absorption, metabolism and excretion. At 120 hr. following administration of a single oral dose, 86% and 15.2% of the administered dose was recovered in the urine and feces, respectively. Following intraperitoneal administration, the excretion was similar but slower. Dogs administered larger doses (17-18 mg/g) orally also excreted most of the material in the urine during the first 24-48 hours (Bratt and Dudley, 1970 cited in 1974 Evaluations of some pesticide residues in food). Using thin-layer chromatography, a total of twelve metabolites were identified in the urine of the two species following single p.o. doses (rats 100 mg/kg; dog 20 mg/kg). No unchanged parent compound was detected in the urine and none of the metabolites had anticholinesterase activity. Five of the twelve metabolites were identified using authentic standards. In both species, 2-ethylamino-4-hydroxy-6-methylpyrimidine was the major urinary metabolite (30% of the dose). Another most predominant metabolite in dog was 4-O-(2-diethylamine-6-methylpyrimidinyl)-beta-D-glucosiduronic acid (11% of dose), and in the rat an unidentified phosphorus-containing product, a possible dealkylated derivative of either pirimiphos-methyl or its oxygen analogue (12% of dose). Other identified urinary metabolites included 2-amino-4-hydroxy-6-methylpyrimidine, 2[-N-ethyl-N-(2-hydroxyethyl) amino]-4-hydroxy-6-methylpyrimidine, and 2-diethylamino-4-hydroxy-6-methylpyrimidine (MRID 00080738, 00080739, 4365801).

II. TOXICOLOGY ENDPOINTS OF CONCERN FOR USE IN RISK ASSESSMENT

On January 12, 1998, the HED Hazard ID SARC evaluated the toxicology data base of pirimiphos-methyl and selected doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments, re-assessed the Reference Dose (RfD) established for chronic dietary risk assessment, and addressed the sensitivity of infants and children from exposure to Pirimiphos-methyl as required by the Food Quality Protection Act (FQPA) of 1996. The Hazard ID SARC's conclusions are presented below.

(1) Acute dietary risk assessment

In the 28-day study, 5 healthy adult human males received gelatin capsules containing Pirimiphos-methyl (97.8%) at a dose of 0.25 mg/kg for 28 days. No biologically significant effects were seen on plasma or erythrocyte ChE inhibition during days 1 through 7. One male subject showed borderline depression of plasma ChE inhibition on days 14 and 28 (-13% and -21%, respectively below predosing measurement). In a follow up 56-day study, 3 healthy adult human males and 4 females received Pirimiphos-methyl(97.8%) at the same dose (0.25 mg/kg) for 56 days. Plasma and erythrocyte cholinesterase activities (ChE inhibition) were measured twice prior to dosing, on days 1, 7, 14, 21, 28, 35, 42, 49 and 56 of dosing as well as on days 7, 14, 21 and 28 post-dosing. No biologically significant effects were seen on plasma or erythrocyte ChE inhibition during days 1 through 3. Statistically significant decreases in plasma ChE inhibition (up to 24%, relative to lowest and/or mean pre-dosing activity) were seen in 3 females between days 14 and 35 (MRID 00080732). Based on lack of cholinesterase inhibition up to day 7,

0.25 mg/kg was considered to be the NOEL for acute effects (i.e., after a single exposure) since ChE inhibition was not observed in either study until day 14. In addition, although no plasma or erythrocyte ChE inhibition was seen in either study, the Committee selected this dose since it was the only dose that was tested and it was presumed that a higher dose could have caused ChE inhibition. Although, the developmental toxicity study in rabbits showed no increased sensitivity in fetuses as compared to maternal animals following *in utero* exposures and the two-generation reproduction toxicity study in rats showed no increased sensitivity in pups when compared to adults, the Hazard ID SARC determined that the FQPA 10 x factor should be retained because of the inadequate data base 1) to evaluate acute delayed neurotoxicity following a single exposure, 2) to assess the functional development of young animals and in turn the susceptibility to infants and children and 3) to determine the need for a developmental neurotoxicity study. The data gaps are listed in Section 7 below. Thus, for acute dietary risk assessment, a margin of Exposure (MOE) of 100 is required. This 100 incudes the conventional 10 x (for use of a human study) and a 10 x under FQPA.

(2) Chronic Dietary [Reference Dose (RfD)]: The RfD established in 1988 was re-assessed by the Hazard ID SARC based on a 56-day oral study with human volunteers (MRID 00080732). In this study, 3 healthy adult human males and 4 females received gelatin capsules containing Pirimiphos-methyl (97.8%) at a dose of 0.25 mg/kg for 56 days. Plasma and erythrocyte cholinesterase activities (ChE inhibition) were measured twice prior to dosing, on days 1, 7, 14, 21, 28, 35, 42, 49 and 56 of dosing as well as on days 7, 14, 21 and 28 post-dosing (recovery period). Statistically significant decreases in plasma ChE inhibition (up to 24%, relative to lowest and/or mean pre-dosing activity) were seen in three females between days 14 and 35. The Hazard ID SARC determined that since only a single dose was tested and significant plasma ChE inhibition was seen in three females between days 14 and 3, this dose should be considered as the LOEL rather than a "threshold" NOEL. Thus, the LOEL was defined as 0.25 mg/kg. Although the developmental toxicity study in rabbits showed no increased sensitivity in fetuses as compared to maternal animals following *in utero* exposures and the two-generation reproduction toxicity study in rats showed no increased sensitivity in pups when compared to adults, the Committee determined that **the FQPA 10 x factor should be retained** because of the inadequate data base 1) to evaluate neurotoxicity following long-term exposure, 2) to assess the functional development of young animals and in turn the susceptibility to infants and children and 3) to determine the need for a developmental neurotoxicity study. In addition to the 10 x for intra-species variation (for use of a human study) and 10 x for FQPA, the Committee also applied an additional 30 x Uncertainty Factor (UF) under FIFRA. The FIFRA UF includes a 3 x for the use of a LOEL and a 10 x for data gaps of a chronic toxicity study in dogs and a chronic toxicity/carcinogenicity study in rats as well as a delayed neurotoxicity study in hens. Thus, for chronic dietary risk assessment, an **UF of 3000 is required** and the RfD is revised as follows:

Revised RfD = [0.25 mg/kg/day (NOEL)] / [3000 (UF)] = 0.00008 mg/kg/day

Occupational/Residential Exposure

Dermal absorption studies are not available. Consequently, the Committee assumed a dermal absorption factor of 100% (default value) for risk assessments. This assumption is supported by 1) the evidence of dermal absorption in the 21-day dermal toxicity where systemic toxicity was seen at the lowest dose tested and 2) the comparison of the LOELs of the oral and dermal toxicity studies based on the same endpoint (cholinesterase inhibition) in the same species (rabbits). In the oral developmental toxicity in New Zealand White rabbits, the maternal LOEL was 24 mg/kg/day based on plasma and erythrocyte cholinesterase inhibition; the maternal NOEL was 12 mg/kg/day (MRID No. 43206301). In the dermal toxicity study in New Zealand White rabbits, the LOEL was 4 mg/kg/day (LDT) based on red blood cell cholinesterase inhibition; a NOEL was not established (MRID No. 00129342).

(3) Short-Term Dermal (1-7 days), Intermediate term (1 week to several months) and Long Term (several months to lifetime) Occupational and Residential Exposure: For short term occupational and residential risk assessment, a NOEL=0.25 mg/kg/day from a 28-day human volunteer study (Acc. 00097671) was recommended. Since plasma or erythrocyte cholinesterase inhibition was not seen during days 1 through 7 (the exposure period of concern), this dose was considered to be the NOEL for this risk assessment (i.e., 1-7 days time period). The Hazard ID SARC did not utilize the results of the 21-day dermal toxicity in rabbits, because of the availability of adequate data in humans. Since an oral dose was identified, a dermal absorption rate of 100% should be used for dermal risk assessments.

For intermediate and long-term occupational and residential risk assessments, a LOEL of 0.25 mg/kg from a 56-day human volunteer study (MRID 00080732) was chosen based on significant plasma ChE inhibition in three female subjects between days 14 and 35 in a 56-day study. Since plasma or erythrocyte cholinesterase inhibition was seen during days 14 and 35, this dose was considered to be the LOEL for this risk assessment. The Hazard ID SARC did not utilize the results of the 21-day dermal toxicity in rabbits, because of the availability of adequate data in humans. Since an oral dose was identified, a dermal absorption rate of 100% should be used for dermal risk assessments.

(4) Short Term, Intermediate Term and Long Term Inhalation Exposure

Except for an acute inhalation toxicity study, the results on which pirimiphos- methyl is placed in Toxicity Category IV (LC_{50} = >5.04 mg/L), no other studies are available via this route. Therefore, the Hazard ID SARC selected an oral dose for inhalation risk assessments. Inhalation risk assessments considered the following steps:

Step I. The inhalation exposure component (i.e.,mg/L) using a 100% absorption rate (default value) should be converted to an equivalent oral dose (mg/kg/day)

Step II. The dermal exposure component (i.e., mg/kg/day) using a 100 % dermal absorption rate should be converted to an equivalent oral dose. This dose should then be combined with the converted oral dose in Step I.

Step III The combined dose from Step II should then be compared to the oral dose of 0.25 mg/kg/day to calculate the MOE's.

The MOE requirements are different for the three time periods because of the use of this dose as a NOEL for Short-Term and as the LOEL for Intermediate-and Long-Term exposure.

Margin of Exposure for Occupational/Residential Exposures:

For Short-Term dermal and inhalation exposure risk assessments, a MOE of 100 is required and includes the conventional 10 x and the FQPA 10 x factors. For this time period, the oral dose is used as the NOEL because cholinesterase

inhibition was *not seen* during the exposure period of concern (i.e., 1-7 days).

For Intermediate-Term dermal and inhalation exposure risk assessments, a MOE of 300 is required and includes the conventional 10 x and the FQPA 10 x as well as an additional 3 x factor under FIFRA. For this time period, the oral dose is used as the LOEL because cholinesterase inhibition *was seen* and thus requiring an additional 3 x factor under FIFRA (i.e., lack of a NOEL in the critical study).

For Long-Term dermal and inhalation exposure risk assessments, a MOE of 3000 is required and includes the conventional 10 x, the FQPA 10 x and an additional 30 x under FIFRA. The 30 x factor under FIFRA includes a 3 x for the use of a LOEL and a 10 x for data gaps of chronic toxicity studies in rats and dogs.

There are no registered residential uses in the current use pattern; however, the Committee determined that the FQPA is relevant for occupational exposure to Pirimiphos-methyl because of the concern for pregnant occupational workers exposed to this organophosphate chemical. The Committee determined that the FQPA 10 x factor should be retained because of the inadequate data base 1) to evaluate neurotoxicity following acute or long-term exposures,

2) to assess the functional development of young animals and in turn the susceptibility to infants and children and 3) to determine the need for a developmental neurotoxicity study. The data gaps are listed on page 16.

Recommendation for Aggregate Exposure Risk Assessments

These are not required since there are no registered residential uses and the use pattern

does not indicate any exposure via drinking or ground water.

(5) CLASSIFICATION OF CARCINOGENIC POTENTIAL The Hazard ID SARC concluded that the carcinogenic potential of Pirimiphos-methyl can not be determined due to lack of an acceptable carcinogenicity study in rats.

(6) Special Sensitivity to Infants and Children: There is no indication of additional sensitivity to young rats or rabbits following pre-and/or postnatal exposure to Pirimiphos-methyl in the developmental and reproductive toxicity studies. Although, the developmental toxicity study in rabbits showed no increased sensitivity in fetuses as compared to maternal animals following *in utero* exposures and the two-generation reproduction toxicity study in rats showed no increased sensitivity in pups when compared to adults, the Committee determined that the FQPA 10 x factor should be retained because of the inadequate data base 1) to evaluate neurotoxicity following acute and long-term exposure, 2) to assess the functional development of young animals and in turn the susceptibility to infants and children and 3) to assess the need for a developmental neurotoxicity study.

(7) Data Gaps: The following data gaps were identified:

1. Acute Delayed Neurotoxicity Study in Hens (§81-7)

2. Chronic Toxicity Study in Dogs (§83-1a)

3. Combined Chronic Toxicity/Carcinogenicity Study in Rats (§83-5)

Cited References

00087032 Howard, J.K. and Gore, C.W. (1976) The Human Response to Long Term Oral Administration of Low Doses of Pirimiphos-Methyl. Chemical Industries, Industrial Hygiene Research Laboratories. Laboratory Report Number MED/76/2B, October 30, 1976. MRID 00080732. Unpublished study.

00080738 Bratt, H. and L.A. Jones. (1973) Pirimiphos-methyl (PP511): Metabolism in Rats and Dogs. Report No. HO/IH/P/81B. Unpublished prepared by Imperial Chemical Industries. 18 p.

00080739 Mills, I.E. (1976) Pirimiphos-methyl: Blood Concentrations and Tissue Retention in the Rat. Report No. CTL/P/247. Unpublished study conducted by Imperial Chemical Industries, Central Toxicology Laboratory, 11p.

00080743 Noel, P.R.B.; Mawdesley-Thomas, L.E.; Rivett, K.F.; et al. (1970) PP 511: Oral Toxicity Studies in Dogs (Initial Studies and Repeated Dosage for Thirteen Weeks): 3258/70/70. (Unpublished study received Dec 1, 1978 under 10182-EX-15; prepared by Huntingdon Research Center, England, submitted by ICI Americas, Inc., Wilmington, Del.; CDL:097671-D)

00097671 Chart, S., Foulkes, C., Gore, C.W. and Williamson (1974) Erythrocyte and Plasma Cholinesterase Activity in Human Volunteers Administered Pirimiphos-Methyl. Imperial Chemical Industries, Industrial Hygiene Research Laboratories, Laboratory Report Number HO/CTL/P/128, August, 1974. Accession No. 0097671. Unpublished study.

00126254 Roberts, N.; Fairley, C.; Almond, R.; et al. (1983) The Sub-chronic Delayed Neurotoxicity of Pirimiphos-methyl to the Domestic Hen: ICI 411 NT/821118. (Unpublished study received Mar 10, 1983 under 10182-EX-15; prepared by Huntingdon Research Center, Eng., submitted by ICI Americas, Inc., Wilmington, DE; CDL:071451-A)

00126256 Done, J.; McGregor, D.; Clark, P.; et al. (1980) Cytogenetic Study in Rats of Pirimiphos-methyl: Inveresk Research International Report No. 1603. (Unpublished study received Mar 10, 1983 under 10182-EX-15; prepared by Inveresk Research International, Eng., submitted by ICI Americas, Inc., Wilmington, DE; CDL: 071451-C)

00126257 Kynoch, S.; Elliott, P.; Liggett, M.; et al. (1981) GFU 053, A 75.4% W/W Formulation of Pirimiphos-methyl: ICI 356, 357, 358, 359, 360/SE, SS,

AC/80549. (Unpublished study received Mar 10, 1983 under 10182-EX-15; prepared by Huntingdon Research Centre, Eng., submitted by ICI Americas, Inc., Wilmington, DE; CDL:071451-D)

00129341 Henderson, C.; Parkinson, G.; Oliver, G.; et al. (1980) Technical Grade Pirimiphos-methyl: Buehler Skin Sensitization Test: [Guinea Pigs]: Report No. CTL/P/499. (Unpublished study received May 19, 1983 under 3F2897; prepared by Imperial Chemical Industries Ltd., Eng., submitted by ICI Americas, Inc., Wilmington, DE; CDL:071621-B)

00129342 Damment, S.; Jones, J.; Glaister, J. (1980) Pirimiphos-Methyl (PP511): A 21 Day Dermal Toxicity Study in the Rabbit: Report No. 2279-38/59. (Unpublished study received May 19, 1983 under 3F2897; prepared by Hazleton Laboratories Europe Ltd., Eng., submitted by ICI Americas, Inc., Wilmington, DE; CDL:071621-C)

00129343 Berry, D.; Gore, C. (1975) Pirimiphos-methyl (PP 511): Determination of No Effect Level during a 28 Day Rat Feeding Study: Report No. CTL/P/199. (Unpublished study received May 19, 1983 under 3F2897; submitted by ICI Americas, Inc., Wilmington, DE; CDL:071621-D)

00144969 Callander, R. (1984) Pirimiphos-Methyl--An Evaluation in the salmonella Mutagenicity Assay: Report No. CTL/P/962. Unpublished study prepared by Imperial chemical Industries PLC. 29 p.

00151623 Killick, M.; Pigott, G.; Banham, P.; et al. (1985) Pirimiphos-methyl: Teratogenicity Study in the Rat: Rep. No. CTL/P/1334. Unpublished study prepared by Imperial Chemical Industries Ltd. 49 p.

41556302 McGregor, D. (1975) Pirimiphos-Methyl: Dominant Lethal Study in Mice of Pirimiphos-Methyl: Lab Project I.D.: CTL/C/291. Unpublished study prepared by Inveresk Research International. 40 p.

41556303 Cross, N. (1985) Pirimiphos-Methyl (Technical Grade): Assessment of Mutagenic Potential Using L5178Y Mouse Lymphoma Cells: Lab Project No.: CTL/C/1437. Unpublished study prepared by ICI Central Toxicology Laboratory. 29 p.

41556304 Lewis, R. (1990) Pirimiphos-Methyl: 4-hour Acute Inhalation Toxicity Study in the Rat: Lab Project I.D.: CTL/P/2795. Unpublished study prepared by ICI Central Toxicity Laboratory, Alderly Park.

55 p.

41599501 Wildgoose, J.; Howard, C.; Richardson, C. (1986) Pirimiphos-Methyl : A Cytogenetic Study in Human Lymphocytes in vitro: Lab Project Number:

CTL/P/1477. Unpublished study prepared by Imperial Chemical Industries Plc. 25 p.

41599502 Howard, C.; Barber, G.; Clay, P.; et al. (1986) Pirimiphos-Methyl: An in vitro Sister Chromatid Exchange Study in Chinese Hamster Lung Fibroblasts: Lab Project Number: CTL/P/1450. Unpublished study prepared by Imperial Chemical Industries PLC. 31 p.

43206301 Barton, S.; Hastings, M. (1994) Pirimiphos-Methyl: Developmental Toxicity Study in Rabbits: Lab Project Number: 490767: WECO-9211. Unpublished study prepared by Inveresk Research International. 308 p.

43594101 Nemec, M. (1995) An Acute Neurotoxicity Study of Pirimiphos-Methyl in Rats: Final Report: Lab Project Numbers: WIL-205006: 94037-WECO. Unpublished study prepared by WIL Research Labs, Inc. 1565 p.

43608201 Nemec, M. (1995) A Subchronic (13-Week) Neurotoxicity Study of Pirimiphos-Methyl in Rats: Final Report: Lab Project Number: WIL-205007: 94038-WECO. Unpublished study prepared by WIL Research Labs, Inc. 1400 p.

43968401 Martin, T.; Atkinson, C.; Walsh, U. (1996) Pirimiphos-Methyl: 78 Week Carcinogenicity Study in Mice With Administration by Diet: Lab Project Number: IRI 451115: WECO-9215: IRI 451120. Unpublished study prepared by Inveresk Research International. 1673 p.

43650801 Barton, S., Hastings, M. (1995) Pirimiphos-Methyl: Two generation Reproduction Study in Rats: Lab Project Number: 490772: WECO-9216; 11196. Unpublished study prepared by Inveresk research International. 400p.

92147014 Guttmann, E. (1990) ICI Americas Inc. Phase 3 Summary of MRID 00080749. Pirimiphos-methyl (PP511): Oral Toxicity Study in Beagle Dogs (Repeated Daily Dosage For Two Years): REF. No. 5438/72/834; CTL Report No. CTL/C/246. Prepared by Huntingdon Research Laboratory. 9p.

92147019 Guttmann, E. (1990) ICI Americas Inc. Phase 3 Summary of MRID 00081912. Pirimiphos-methyl (PP511): 2 Year Feeding Study in the Rat: CTL Report No. HO/IH/P/113; CTL Study No. PR0045. Prepared by ICI Central Toxicology Laboratory. 10 p.

92147032 Hunter, B.; Graham, C.; Street, A. et al. (1990) ICI Americas Inc. Phase 3 Reformat of MRID 00080746. Long-Term Feeding of Pirimiphos-methyl (PP511) in Mice; CTL Report No. CTL/C/340; REF. NO. ICI 34/7658. Prepared by Huntingdon Research Center. 408 p.

92147035 Gore, C.; Griffiths, D.; Phillips, C. et al. (1990) ICI Americas Inc. Phase 3 Reformat of MRID 00081912. Pirimiphos-methyl (PP511): 2 Year Feeding Study in the Rat: (Revised 4th July 1979): CTL Report No. HO/IH/P/113; CTL Study No. PR0045. Prepared by ICI Central Toxicology Laboratory. 590 p.

92147036 Rivett, K.; Edwards, D.; Street, A. et al. (1990) ICI Americas Inc. Phase 3 Reformat of MRID 00080749. Pirimiphos-methyl (PP511): Oral Toxicity Study in Beagle Dogs (Repeated Daily Dosage for Two Years): Huntingdon Research Centre Reference No. 5438/72/834; CTL Report No. CTL/C/246. Prepared by Huntingdon Research Center. 133 p.

- - PIRIMIPHOS-METHYL: - Report of the Hazard Identification Assessment Review Committee. January 29, 1998.

- - EPA (1992). Pirimiphos-methyl: Clarification of FIFRA 88 data Requirements. Memorandum from Marion Copley and John Doherty, Health Effects Division to Briscoe/Ellenberger, Special Review and Reregistration Division, dated March 12, 1992. HED Doc. 009381.

- - Rajini, P.S., Muralidhara, M.K., Krishnakumari, and Majumder, S.K. (1986). Mutagenic properties of pirimiphos-methyl in male mice. Bull. Environ. Contam. Toxicol. 36:680-684.

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